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EXAMINER	
THOMAS, DAVID C	
ART UNIT	PAPER NUMBER
1637	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	01/04/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	10/734,622	LIM ET AL.	
	Examiner	Art Unit	
	David C. Thomas	1637	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *23 October 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-45* is/are pending in the application.

4a) Of the above claim(s) *8-14,19,20,24-29 and 36-39* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-7,15-18,21-23,30-35 and 40-45* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *30 June 2004*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. Applicant's election without traverse of Group I, claims 1-23 and 30-35, and 40-42 (original) and 43-45 (added after the original election response), in the reply filed on November 14, 2005 is acknowledged. Claims 24-29 and 36-39 are withdrawn from the current examination. Claims 40-42 are maintained in the Group I since they are drawn to methods for repertoire determining of a lymphocyte B population using the kit of Group II. Applicants also elected the SEQ ID Nos. 11 and 13 in the VH forward primer group, SEQ ID Nos. 16 and 17 in the JH forward primer group, and SEQ ID Nos. 34 and 35 in the CH probe group. Claims 5-7, 15-18, 21-23, 30-35, and 43-45 read on the elected sequences, while claims 8-14, 19, and 20 read on non-elected sequences. Consequently, claims 1-7, 15-18, 21-23, 30-35, and 40-45 will be examined on the merits.

Claim Objections

2. Claim 23 is objected to under 37 CFR 1.75 as being a substantial duplicate of claim 6. When two claims in an application are duplicates or else are so close in content that they both cover the same thing, despite a slight difference in wording, it is proper after allowing one claim to object to the other as being a substantial duplicate of the allowed claim. See MPEP § 706.03(k).

Claim Rejections - 35 USC § 112

3. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

4. Claims 40-42 provide for the use of a kit for the in vitro diagnosis of a condition associated with an abnormal expression of the repertoire of a given type of an immunoglobulin heavy chain by a lymphocyte b population in a subject, but since the claim does not set forth any steps involved in the method/process, it is unclear what method/process applicant is intending to encompass. A claim is indefinite where it merely recites a use without any active, positive steps delimiting how this use is actually practiced.

Claims 40-42 are rejected under 35 U.S.C. 101 because the claimed recitation of a use, without setting forth any steps involved in the process, results in an improper definition of a process, i.e., results in a claim which is not a proper process claim under 35 U.S.C. 101. See for example *Ex parte Dunki*, 153 USPQ 678 (Bd.App. 1967) and *Clinical Products, Ltd.* v. *Brenner*, 255 F. Supp. 131, 149 USPQ 475 (D.D.C. 1966).

Claim Rejections - 35 USC § 102

5. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

6. Claims 1, 2, and 4 are rejected under 35 U.S.C. 102(b) as being anticipated by Delassus et al. (J. Immunolog. Meth. (1995) 219-229).

Delassus teaches a process for determining the quantitative and qualitative profile of the repertoire of a given type of an immunoglobulin heavy chain expressed by a lymphocyte B population present in a tissue sample (analysis of repertoire in B cells is

studied at mRNA and DNA levels, p. 220, column 1, line 43 to column 2, line 8), characterized in that it comprises the following steps:

(a) obtaining either the cDNA from the mRNA expressed from the tissue sample or the cellular DNA extract of the tissue sample (RNA and DNA was extracted from splenic cells and purified by cesium chloride gradients, p. 220, column 2, line 37 to p. 221, column 1, line 3; cDNA was obtained after reverse transcription of RNA, page 221, column 1, lines 4-8);

(b) performing the amplification of the cDNA obtained at the step (a) with a set of VH forward primers capable of specifically hybridizing in stringent conditions with the nucleic acids encoding the variable segments (VH) of immunoglobulin heavy chains, said variable segments being distributed among VH subgroups (sense primers specific for VH families J558, Q52, and 7183 were used in amplification, p. 222, column 1, lines 12-24, p. 223, column 1, lines 6-14 and p. 224, column 1, lines 8-14), associated with a CH reverse primer, or a mixture thereof, capable of specifically hybridizing in stringent conditions with the nucleic acid encoding the constant segment (CH) of a given type of an immunoglobulin heavy chain (antisense primer was used specific for either IgM or IgG constant region, p. 221, column 1, lines 25-28, p. 223, column 1, lines 6-14 and p. 224, column 1, lines 8-14); and

(c) determining the quantitative and qualitative profile of the repertoire of said type of immunoglobulin heavy chain for each VH subgroup (to quantify PCR products, run-off reaction was performed on PCR products using a labeled primer and known size standards, and resolved on sequencing gels and for imaging and analysis of peak

heights by software, p. 222, column 1, line 29 to column 2, line 4, p. 223, column 1, lines 14-32, and Figure 1; quality of products was analyzed by direct sequence analysis, which yields data on both lengths and composition of products, p. 222, column 2, lines 41-43 and Figure 4).

With regard to claim 2, Delassus teaches the process for determining the quantitative and qualitative profile characterized in that separated amplifications are performed for each of the VH subgroups (PCR reactions were performed for each of three different variable gene families, p. 222, column 1, lines 8-14 and p. 223, lines 6-14).

With regard to claim 4, Delassus teaches the process for determining the quantitative and qualitative profile characterized in that the separated amplification products obtained for each of the VH subgroups are further elongated using a CH labeled reverse probe capable of specifically hybridizing in stringent conditions with the constant segment of the given type of immunoglobulin heavy chain and capable of emitting a detectable signal (fluorescently-labeled probe, XIgM, specific for the IgM constant region, was used for run-off assays, p. 221, column 2, lines 9-13 and 22 and p. 222, column 2, lines 26-31) and characterized in that the elongation products are separated, for each of the VH subgroups, relative to their length (run-off products are resolved on gel, p. 222, column 2, lines 1-4 and p. 223, column 1, lines 23-24), the signal obtained for the separated elongation products in measured, and the quantitative and qualitative profile of the labeling intensity relative to the elongation product length is established, for each of the VH subgroups individually (software used to quantify gel

image peak intensities to generate profiles for repertoire analysis, p. 223, column 1, lines 24-32 and Figures 1 and 2; quality of products was analyzed by direct sequence analysis, p. 222, column 2, lines 41-43 and Figure 4).

Claim Rejections - 35 USC § 103

7. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

8. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

9. Claim 3 is rejected under 35 U.S.C. 103(a) as being unpatentable over Delassus et al. (J. Immunolog. Meth. (1995) 219-229) in view of Jacobsen et al. (J. Infectious Dis. (2003) 187;963-973).

Delassus teaches the limitations of claims 1, 2, and 4 as discussed above.

Delassus does not teach a method for determining the quantitative and qualitative profile characterized in that the separated amplifications are real-time

separated amplifications using a CH labeled reverse probe such as a hydrolysis probe capable of specifically hybridizing in stringent conditions with the constant segment of the given type of immunoglobulin heavy chain and capable of emitting a detectable signal every time each amplification cycle occurs, and characterized in that the signal obtained for each VH subgroup is measured.

With regard to claim 3, Jacobsen teaches a quantitative real-time PCR assay to measure clonotypic genes by quantifying the B chain variable and constant regions of T cell receptors using primers and probes specific for each target sequence (p. 965, column 1, lines 21-36, p. 969, column 2, lines 13-18, and Figure 4). The TaqMan probes used to detect the constant region amplification products was 5'-end-labeled with FAM as a reporter and 3'-end-labeled with TAMRA as a quencher and used in real-time assays using the ABI Prism 7000 Sequence Detection System to measure cycle thresholds during the 40 cycles of the amplification (p. 965, column 1, lines 37-51).

Jacobsen does not teach a method for determining the quantitative and qualitative profile of the repertoire of a given type of an immumoglobulin heavy chain expressed by a lymphocyte B population using a VH and CH primer for amplification of each heavy chain type.

It would have been prima facie obvious to one having ordinary skill in the art at the time the invention was made to combine the methods of Delassus for PCR analysis of the immunoglobulin heavy chain repertoire and those of Jacobsen for real-time PCR amplification of variable and constant gene regions of immunoglobulin genes since the ability to analyze products in real-time is faster and more quantitative than conventional

analytical techniques such as gel electrophoresis, since standard curves can be generated using internal control targets for more precise quantification. Thus, an ordinary practitioner would have been motivated to combine the methods of Delassus and Jacobsen to perform a real-time assay to determine quantitative profiles of the heavy chain repertoire expressed by a lymphocyte B population. Furthermore, real-time analysis allows samples to be contained during real-time PCR, reducing the risk of carry-over contamination since reaction vessels need not be opened for loading gels. The real-time assay also makes the analysis more suitable for high-throughput assays when preparing large numbers of samples.

10. Claims 5-7, 23 and 43 are rejected under 35 U.S.C. 103(a) as being unpatentable over Delassus et al. (J. Immunolog. Meth. (1995) 219-229) in view of Honjo et al. (U.S. Patent No. 6,096,878) and further in view of Buck (BioTechniques (1999) 27:528-536).

Delassus teaches the limitations of claims 1, 2, and 4 as discussed above.

With regard to claim 7, Delassus also teaches a CH reverse primer capable of specifically hybridizing in stringent conditions with the nucleic acids encoding the constant segments (CH) of the IgM heavy chain (antisense primer was used specific for either IgM or IgG constant region, p. 221, column 1, lines 25-28, p. 223, column 1, lines 6-14 and p. 224, column 1, lines 8-14).

Delassus does not teach a process for determining the quantitative and qualitative profile using a VH4 primer having the sequences of SEQ ID No. 11, and a VH5 primer having the sequence of SEQ ID No. 13.

With regard to claims 5-7, 23, and 43, Honjo teaches DNA fragments containing segments of the human immunoglobulin VH gene containing the sequences of SEQ ID No. 11 (positions 469-490 of SEQ ID No. 31) and SEQ ID No. 13 (positions 338-355 of SEQ ID No. 51).

Honjo does not teach a method for determining the quantitative and qualitative profile of the repertoire of a given type of an immumoglobulin heavy chain expressed by a lymphocyte B population using a VH and CH primer for amplification of each heavy chain type.

It would have been prima facie obvious to one having ordinary skill in the art at the time the invention was made to combine the method of Delassus for PCR analysis of the immunoglobulin heavy chain repertoire in view of Honjo because Honjo teaches fragments containing VH sequences that can used to design forward PCR primers for amplification of the variable gene repertoire. Thus, an ordinary practitioner would have been motivated to use the target region utilized by Honjo for defining sequences containing one or more segments of the VH gene. Since the methods of Honjo provides for a series of VH segments distributed among the various VH subgroups, primers can be designed to represent the desired subgroup and paired with JH or CH region primers for amplification. Furthermore, the segments provide sequences for design of labeled VH probes if real-time analysis is to be performed.

In the recent court decision *In Re Deuel* 34 USPQ 2d 1210 (Fed. Cir. 1995), the Court of Appeals for the Federal Circuit determined that the existence of a general

method of identifying a specific DNA does not make the specific DNA obvious.

Regarding structural or functional homologs, however, the Court stated,

"Normally, a *prima facie* case of obviousness is based upon structural similiarity, i.e., an established structural relationship between a prior art compound and the claimed compound. Structural relationships may provide the requisite motivation or suggestion to modify known compounds to obtain new compounds. For example, a prior art compound may suggest its homologs because homologs often have similar properties and therefore chemists of ordinary skill would ordinarily contemplate making them to try to obtain compounds with improved properties (see page 9, paragraph 4 of attached ref)."

Since the claimed primers simply represent structural homologs of the oligonucleotides taught by Honjo, which are 100% derived from sequences expressly suggested by the prior art of Honjo as useful for primers for the amplification of VH genes, and concerning which a biochemist of ordinary skill would attempt to obtain alternate compounds with improved properties, the claimed primers are *prima facie* obvious over the cited references in the absence of secondary considerations.

With regard to the issue of equivalence of the primers, MPEP 2144.06 notes " Substituting equivalents known for the same purpose. In order to rely on equivalence as a rationale supporting an obviousness rejection, the equivalency must be recognized in the prior art, and cannot be based on applicant's disclosure or the mere fact that the components at issue are functional or mechanical equivalents. An express suggestion to substitute one equivalent component or process for another is not necessary to render such substitution obvious. In re Fout , 675 F.2d 297, 213 USPQ 532 (CCPA 1982)."

With regard to the issue of reasonable expectation of success in using such equivalents, Buck expressly provides evidence of the equivalence of primers.

Specifically, Buck invited primer submissions from a number of labs (39) (page 532, column 3), with 69 different primers being submitted (see page 530, column 1). Buck also tested 95 primers spaced at 3 nucleotide intervals along the entire sequence at issue, thereby testing more than 1/3 of all possible 18 mer primers on the 300 base pair sequence (see page 530, column 1). When Buck tested each of the primers selected by the methods of the different labs, Buck found that EVERY SINGLE PRIMER worked (see page 533, column 1). Only one primer ever failed, No. 8, and that primer functioned when repeated. Further, EVERY SINGLE CONTROL PRIMER functioned as well (see page 533, column 1). Buck expressly states "The results of the empirical sequencing analysis were surprising in that nearly all of the primers yielded data of extremely high quality (page 535, column 2)." Therefore, Buck provides direct evidence that all primers would be expected to function, and in particular, all primers selected according to the ordinary criteria, however different, used by 39 different laboratories. It is particularly striking that all 95 control primers functioned, which represent 1/3 of all possible primers in the target region. This clearly shows that every primer would have a reasonable expectation of success.

11. Claim 15 is rejected under 35 U.S.C. 103(a) as being unpatentable over Delassus et al. (J. Immunolog. Meth. (1995) 219-229) in view of Flanagan et al. (EMBO J. (1982) 1:655-660) and further in view of Jacobsen et al. (J. Infectious Dis. (2003) 187;963-973) and further in view of Buck (BioTechniques (1999) 27:528-536).

Delassus teaches the limitations of claims 1, 2, and 4 as discussed above.

Delassus does not teach a CH labeled hydrolysis-probe that has the sequence SEQ ID No. 34, or the sequence SEQ ID No. 34 wherein at least one point mutation may occur.

Flanagan teaches a sequence of the epsilon heavy chain constant gene that contains a sequence homologous to the first 8 of 9 nucleotides of SEQ ID No. 34 at positions 107-115 and thus may serve as a hydrolysis probe wherein at least one point mutation may occur (Figure 4).

Flanagan does not teach a method for determining the quantitative and qualitative profile of the repertoire of a given type of an immumoglobulin heavy chain expressed by a lymphocyte B population using a VH and CH primer for amplification of each heavy chain type.

It would have been prima facie obvious to one having ordinary skill in the art at the time the invention was made to combine the method of Delassus for PCR analysis of the immunoglobulin heavy chain repertoire in view of Jacobsen for real-time PCR amplification of variable and constant gene regions of immunoglobulin genes and further in view of Flanagan because Flanagan teaches constant region gene sequences that can used to design PCR primers or probes for amplification and analysis of the variable gene repertoire using VH and CH primers. Thus, an ordinary practitioner would have been motivated to use the target region utilized by Flanagan for defining sequences containing segments of the CH gene that can serve as primers or probes for real-time analysis in the assay of Delassus for repertoire determination. When further combined with methods of Jacobsen, the repertoire determination can be performed in

real time, which has the advantages of being faster and more quantitative than conventional analytical techniques such as gel electrophoresis, since standard curves can be generated using internal control targets for more precise quantification. Furthermore, real-time analysis allows samples to be contained during real-time PCR, reducing the risk of carry-over contamination since reaction vessels need not be opened for loading gels. The real-time assay also makes the analysis more suitable for high-throughput assays when preparing large numbers of samples.

In the recent court decision *In Re Deuel* 34 USPQ 2d 1210 (Fed. Cir. 1995), the Court of Appeals for the Federal Circuit determined that the existence of a general method of identifying a specific DNA does not make the specific DNA obvious. Regarding structural or functional homologs, however, the Court stated,

"Normally, a *prima facie* case of obviousness is based upon structural similiarity, i.e., an established structural relationship between a prior art compound and the claimed compound. Structural relationships may provide the requisite motivation or suggestion to modify known compounds to obtain new compounds. For example, a prior art compound may suggest its homologs because homologs often have similar properties and therefore chemists of ordinary skill would ordinarily contemplate making them to try to obtain compounds with improved properties (see page 9, paragraph 4 of attached ref)."

Since the claimed primers and probes simply represent structural homologs of the oligonucleotides taught by Flanagan, which are 100% derived from sequences expressly suggested by the prior art of Flanagan as useful for primers or probes for the real-time PCR amplification of VH genes, and concerning which a biochemist of ordinary skill would attempt to obtain alternate compounds with improved properties, the claimed primers are *prima facie* obvious over the cited references in the absence of secondary considerations.

With regard to the issue of equivalence of the primers, MPEP 2144.06 notes " Substituting equivalents known for the same purpose. In order to rely on equivalence as a rationale supporting an obviousness rejection, the equivalency must be recognized in the prior art, and cannot be based on applicant's disclosure or the mere fact that the components at issue are functional or mechanical equivalents. An express suggestion to substitute one equivalent component or process for another is not necessary to render such substitution obvious. In re Fout , 675 F.2d 297, 213 USPQ 532 (CCPA 1982)."

With regard to the issue of reasonable expectation of success in using such equivalents, Buck expressly provides evidence of the equivalence of primers. Specifically, Buck invited primer submissions from a number of labs (39) (page 532, column 3), with 69 different primers being submitted (see page 530, column 1). Buck also tested 95 primers spaced at 3 nucleotide intervals along the entire sequence at issue, thereby testing more than 1/3 of all possible 18 mer primers on the 300 base pair sequence (see page 530, column 1). When Buck tested each of the primers selected by the methods of the different labs, Buck found that EVERY SINGLE PRIMER worked (see page 533, column 1). Only one primer ever failed, No. 8, and that primer functioned when repeated. Further, EVERY SINGLE CONTROL PRIMER functioned as well (see page 533, column 1). Buck expressly states "The results of the empirical sequencing analysis were surprising in that nearly all of the primers yielded data of extremely high quality (page 535, column 2)." Therefore, Buck provides direct evidence that all primers would be expected to function, and in particular, all primers selected

according to the ordinary criteria, however different, used by 39 different laboratories. It is particularly striking that all 95 control primers functioned, which represent 1/3 of all possible primers in the target region. This clearly shows that every primer would have a reasonable expectation of success.

12. Claims 16, 17, 21, and 45 are rejected under 35 U.S.C. 103(a) as being unpatentable over Delassus et al. (J. Immunolog. Meth. (1995) 219-229) in view of Chang (U.S. Patent No. 5,326,696) and further in view of Buck (BioTechniques (1999) 27:528-536).

Delassus teaches the limitations of claims 1, 2, and 4 as discussed above.

With regard to claims 17 and 21, Delassus also teaches a process for determining the quantitative and qualitative profile characterized in that fluorescently-labeled JH antisense primers that bind to junction segments are used in elongation assays with products previously amplified with VH forward primers for each family (p. 223, column 1, lines 14-23) and characterized in that the elongation products are separated, for each of the JH subgroups, relative to their length (run-off products are resolved on gel, p. 222, column 2, lines 1-4 and p. 223, column 1, lines 23-24), the signal obtained for the separated elongation products in measured, and the quantitative and qualitative profile of the labeling intensity relative to the elongation product length is established, for each of the JH subgroups for the given VH subgroups (software used to quantify gel image peak intensities to generate profiles for repertoire analysis, p. 223, column 1, lines 24-32 and Figures 1 and 2; quality of products was analyzed by direct sequence analysis, p. 222, column 2, lines 41-43 and Figure 4)..

Delassus does not teach a process for determining the quantitative and qualitative profile characterized in that, when the given type of immunoglobulin heavy chain is an IgG heavy chain and when the separated amplification products obtained for each of the VH subgroups are further elongated, the CH labeled reverse probe has the sequence SEQ ID No. 35, or the sequence SEQ ID No. 35 wherein one to three point mutations may occur, except for the nucleotides 1 to 6 of its 3' part.

With regard to claims 16, 17, 21, and 45, Chang teaches a 3'-primer sequence used for amplification of VH genes that contains the sequence of SEQ ID. No. 35 (column 8, lines 44-51; SEQ ID No. 13, positions 2-23).

Chang does not teach a method for determining the quantitative and qualitative profile of the repertoire of a given type of an immumoglobulin heavy chain expressed by a lymphocyte B population using a VH and CH primer for amplification of each heavy chain type.

It would have been prima facie obvious to one having ordinary skill in the art at the time the invention was made to combine the method of Delassus for PCR analysis of the immunoglobulin heavy chain repertoire in view of Chang because Chang teaches a primer sequence specific to the constant gene that can used to design PCR primers or probes for amplification of the variable gene repertoire. Thus, an ordinary practitioner would have been motivated to use the primer sequence taught by Chang for designing primers or labeled probes for real-time analysis since a primer based on this sequence has been used successfully for VH and VL amplification (Chang, column 8, lines 43-51).

In the recent court decision *In Re Deuel* 34 USPQ 2d 1210 (Fed. Cir. 1995), the Court of Appeals for the Federal Circuit determined that the existence of a general method of identifying a specific DNA does not make the specific DNA obvious. Regarding structural or functional homologs, however, the Court stated,

"Normally, a *prima facie* case of obviousness is based upon structural similiarity, i.e., an established structural relationship between a prior art compound and the claimed compound. Structural relationships may provide the requisite motivation or suggestion to modify known compounds to obtain new compounds. For example, a prior art compound may suggest its homologs because homologs often have similar properties and therefore chemists of ordinary skill would ordinarily contemplate making them to try to obtain compounds with improved properties (see page 9, paragraph 4 of attached ref)."

Since the claimed primers simply represent structural homologs of the oligonucleotides taught by Chang, which are 100% derived from sequences expressly suggested by the prior art of Chang as useful for primers for the amplification of VH genes, and concerning which a biochemist of ordinary skill would attempt to obtain alternate compounds with improved properties, the claimed primers are *prima facie* obvious over the cited references in the absence of secondary considerations.

With regard to the issue of equivalence of the primers, MPEP 2144.06 notes " Substituting equivalents known for the same purpose. In order to rely on equivalence as a rationale supporting an obviousness rejection, the equivalency must be recognized in the prior art, and cannot be based on applicant's disclosure or the mere fact that the components at issue are functional or mechanical equivalents. An express suggestion to substitute one equivalent component or process for another is not necessary to render such substitution obvious. In re Fout , 675 F.2d 297, 213 USPQ 532 (CCPA 1982)."

With regard to the issue of reasonable expectation of success in using such equivalents, Buck expressly provides evidence of the equivalence of primers. Specifically, Buck invited primer submissions from a number of labs (39) (page 532, column 3), with 69 different primers being submitted (see page 530, column 1). Buck also tested 95 primers spaced at 3 nucleotide intervals along the entire sequence at issue, thereby testing more than 1/3 of all possible 18 mer primers on the 300 base pair sequence (see page 530, column 1). When Buck tested each of the primers selected by the methods of the different labs, Buck found that EVERY SINGLE PRIMER worked (see page 533, column 1). Only one primer ever failed, No. 8, and that primer functioned when repeated. Further, EVERY SINGLE CONTROL PRIMER functioned as well (see page 533, column 1). Buck expressly states "The results of the empirical sequencing analysis were surprising in that nearly all of the primers yielded data of extremely high quality (page 535, column 2)." Therefore, Buck provides direct evidence that all primers would be expected to function, and in particular, all primers selected according to the ordinary criteria, however different, used by 39 different laboratories. It is particularly striking that all 95 control primers functioned, which represent 1/3 of all possible primers in the target region. This clearly shows that every primer would have a reasonable expectation of success.

13. Claim 18 is rejected under 35 U.S.C. 103(a) as being unpatentable over Delassus et al. (J. Immunolog. Meth. (1995) 219-229) in view of Chang (U.S. Patent No. 5,326,696) and further in view of Jacobsen et al. (J. Infectious Dis. (2003) 187;963-973) and further in view of Buck (BioTechniques (1999) 27:528-536).

Delassus teaches the limitations of claims 1, 2, and 4 as discussed above.

Delassus does not teach a method determining the quantitative and qualitative profile characterized in that the further separated amplifications are real-time amplifications performed using a VH labeled forward probe, preferably a VH labeled forward hydrolysis-probe, capable of specifically hybridizing in stringent conditions with the variable segment of the given type of immunoglobulin heavy chain and capable of emitting a detectable signal every time each amplification cycle occurs, and characterized in that the signal obtained for each of the JH subgroups is measured.

It would have been prima facie obvious to one having ordinary skill in the art at the time the invention was made to combine the method of Delassus for PCR analysis of the immunoglobulin heavy chain repertoire in view of Jacobsen for real-time analysis and in view of Chang because Chang teaches a primer sequence specific to the constant gene that can used to design PCR primers or probes for amplification of the variable gene repertoire. Furthermore, Delassus teaches the use of labeled probes for analysis of amplification products (p. 221, column 2, lines 14-25), and also sequences that can be used as probes that would hybridize to the variable region (p. 221, column 1, lines 12-39). Thus, an ordinary practitioner would have been motivated to use the primer sequence taught by Chang for designing primers or labeled probes for real-time analysis since a primer based on this sequence has been used successfully for VH and VL amplification (Chang, column 8, lines 43-51). When further combined with methods of Jacobsen, the repertoire determination can be performed in real time, which has the advantages of being faster and more quantitative than conventional analytical

techniques such as gel electrophoresis, since standard curves can be generated using internal control targets for more precise quantification. Furthermore, real-time analysis allows samples to be contained during real-time PCR, reducing the risk of carry-over contamination since reaction vessels need not be opened for loading gels. The real-time assay also makes the analysis more suitable for high-throughput assays when preparing large numbers of samples.

In the recent court decision *In Re Deuel* 34 USPQ 2d 1210 (Fed. Cir. 1995), the Court of Appeals for the Federal Circuit determined that the existence of a general method of identifying a specific DNA does not make the specific DNA obvious. Regarding structural or functional homologs, however, the Court stated,

"Normally, a *prima facie* case of obviousness is based upon structural similiarity, i.e., an established structural relationship between a prior art compound and the claimed compound. Structural relationships may provide the requisite motivation or suggestion to modify known compounds to obtain new compounds. For example, a prior art compound may suggest its homologs because homologs often have similar properties and therefore chemists of ordinary skill would ordinarily contemplate making them to try to obtain compounds with improved properties (see page 9, paragraph 4 of attached ref)."

Since the claimed primers simply represent structural homologs of the oligonucleotides taught by Chang, which are 100% derived from sequences expressly suggested by the prior art of Chang as useful for primers for the amplification of VH genes, and concerning which a biochemist of ordinary skill would attempt to obtain alternate compounds with improved properties, the claimed primers are *prima facie* obvious over the cited references in the absence of secondary considerations.

With regard to the issue of equivalence of the primers, MPEP 2144.06 notes " Substituting equivalents known for the same purpose. In order to rely on equivalence

as a rationale supporting an obviousness rejection, the equivalency must be recognized in the prior art, and cannot be based on applicant's disclosure or the mere fact that the components at issue are functional or mechanical equivalents. An express suggestion to substitute one equivalent component or process for another is not necessary to render such substitution obvious. In re Fout , 675 F.2d 297, 213 USPQ 532 (CCPA 1982)."

With regard to the issue of reasonable expectation of success in using such equivalents, Buck expressly provides evidence of the equivalence of primers. Specifically, Buck invited primer submissions from a number of labs (39) (page 532, column 3), with 69 different primers being submitted (see page 530, column 1). Buck also tested 95 primers spaced at 3 nucleotide intervals along the entire sequence at issue, thereby testing more than 1/3 of all possible 18 mer primers on the 300 base pair sequence (see page 530, column 1). When Buck tested each of the primers selected by the methods of the different labs, Buck found that EVERY SINGLE PRIMER worked (see page 533, column 1). Only one primer ever failed, No. 8, and that primer functioned when repeated. Further, EVERY SINGLE CONTROL PRIMER functioned as well (see page 533, column 1). Buck expressly states "The results of the empirical sequencing analysis were surprising in that nearly all of the primers yielded data of extremely high quality (page 535, column 2)." Therefore, Buck provides direct evidence that all primers would be expected to function, and in particular, all primers selected according to the ordinary criteria, however different, used by 39 different laboratories. It is particularly striking that all 95 control primers functioned, which represent 1/3 of all

possible primers in the target region. This clearly shows that every primer would have a reasonable expectation of success.

14. Claims 22 and 44 are rejected under 35 U.S.C. 103(a) as being unpatentable over Delassus et al. (J. Immunolog. Meth. (1995) 219-229) in view of Robinson et al. (U.S. Patent No. 6,652,852) and further in view of Buck (BioTechniques (1999) 27:528-536).

Delassus teaches the limitations of claims 1, 2, and 4 as discussed above.

Delassus does not teach a process for determining the quantitative and qualitative profile characterized in that the set of JH forward primers, optionally labeled, comprises at least the 2 following subgroups of JH primers corresponding to the JH subgroups: the JH1 primers having the sequences SEQ ID No. 16, and the JH2 primer having the sequence SEQ ID No. 17.

With regard to claims 22 and 44, Robinson teaches sequences of the JH1 and JH2 regions that contain the sequences of SEQ ID. No. 16 (column 6, lines 12-14; SEQ ID No. 1, positions 29-13) and SEQ ID No. 17 (column 6, lines 12-14; SEQ ID No. 2, positions 30-13).

Robinson does not teach a method for determining the quantitative and qualitative profile of the repertoire of a given type of an immumoglobulin heavy chain expressed by a lymphocyte B population using a VH and CH primer for amplification of each heavy chain type.

It would have been prima facie obvious to one having ordinary skill in the art at the time the invention was made to combine the method of Delassus for PCR analysis

of the immunoglobulin heavy chain repertoire in view of Robinson because Robinson teaches sequences specific to the JH gene region that can used to design PCR primers or probes for amplification of the variable gene repertoire. Thus, an ordinary practitioner would have been motivated to use the sequences taught by Robinson for designing primers or labeled probes for real-time analysis since a primer based on this sequence can be used to measure each of the JH subgroups in combination with the VH subgroups when amplified using VH and JH primers, or when performing run-off assays using labeled JH probes (Delassus, p. 223, column 1, lines 14-23).

In the recent court decision *In Re Deuel* 34 USPQ 2d 1210 (Fed. Cir. 1995), the Court of Appeals for the Federal Circuit determined that the existence of a general method of identifying a specific DNA does not make the specific DNA obvious. Regarding structural or functional homologs, however, the Court stated,

"Normally, a *prima facie* case of obviousness is based upon structural similiarity, i.e., an established structural relationship between a prior art compound and the claimed compound. Structural relationships may provide the requisite motivation or suggestion to modify known compounds to obtain new compounds. For example, a prior art compound may suggest its homologs because homologs often have similar properties and therefore chemists of ordinary skill would ordinarily contemplate making them to try to obtain compounds with improved properties (see page 9, paragraph 4 of attached ref)."

Since the claimed primers simply represent structural homologs of the oligonucleotides taught by Robinson, which are 100% derived from sequences expressly suggested by the prior art of Robinson as useful for primers and probes for the amplification and quantification of VH genes, and concerning which a biochemist of ordinary skill would attempt to obtain alternate compounds with improved properties, the

claimed primers are *prima facie* obvious over the cited references in the absence of secondary considerations.

With regard to the issue of equivalence of the primers, MPEP 2144.06 notes " Substituting equivalents known for the same purpose. In order to rely on equivalence as a rationale supporting an obviousness rejection, the equivalency must be recognized in the prior art, and cannot be based on applicant's disclosure or the mere fact that the components at issue are functional or mechanical equivalents. An express suggestion to substitute one equivalent component or process for another is not necessary to render such substitution obvious. In re Fout , 675 F.2d 297, 213 USPQ 532 (CCPA 1982)."

With regard to the issue of reasonable expectation of success in using such equivalents, Buck expressly provides evidence of the equivalence of primers. Specifically, Buck invited primer submissions from a number of labs (39) (page 532, column 3), with 69 different primers being submitted (see page 530, column 1). Buck also tested 95 primers spaced at 3 nucleotide intervals along the entire sequence at issue, thereby testing more than 1/3 of all possible 18 mer primers on the 300 base pair sequence (see page 530, column 1). When Buck tested each of the primers selected by the methods of the different labs, Buck found that EVERY SINGLE PRIMER worked (see page 533, column 1). Only one primer ever failed, No. 8, and that primer functioned when repeated. Further, EVERY SINGLE CONTROL PRIMER functioned as well (see page 533, column 1). Buck expressly states "The results of the empirical sequencing analysis were surprising in that nearly all of the primers yielded data of

extremely high quality (page 535, column 2)." Therefore, Buck provides direct evidence that all primers would be expected to function, and in particular, all primers selected according to the ordinary criteria, however different, used by 39 different laboratories. It is particularly striking that all 95 control primers functioned, which represent 1/3 of all possible primers in the target region. This clearly shows that every primer would have a reasonable expectation of success.

15. Claims 30-35 are rejected under 35 U.S.C. 103(a) as being unpatentable over Delassus et al. (J. Immunolog. Meth. (1995) 219-229) in view of Even et al. (Res. Immunol. (1995) 146, 65-80).

Delassus teaches the limitations of claims 1, 2, and 4 as discussed above.

Delassus does not teach a method for the in vitro diagnosis of or the in vitro follow-up of a condition associated with an abnormal expression of the repertoire of a given type of an immunoglobulin heavy chain by a lymphocyte B population in a subject such as an auto-immune disease, a B cell lymphoma or an immunodepressive disease or resulting from a bone marrow transplantation, a vaccinal test or an allergic reaction.

With regard to claim 30, Even teaches a method for the in vitro diagnosis of a condition associated with an abnormal expression of the repertoire of a given type of T cell receptor by a T lymphocyte population in a subject (p. 67, column 1, lines 7-15), characterized in that it comprises the following steps:

(1) determining the quantitative and qualitative profile of the given type of β–chain from a tissue sample of said subject according to anyone of claims I to 23 (profiles of β–chain repertoires were determined from cDNA obtained from total RNA by

reverse transcription by amplification using one of 24 Vβ subfamily-specific primers and one Cβ-specific primer, and quantified using a run-off assay, p. 69, column 2, lines 5-22 and Table I),

(2) comparing the quantitative and qualitative profile obtained at the step (1) with a control quantitative and qualitative profile of said given type of immunoglobulin heavy chain, the demonstration of a significant modification of the profile obtained at the step (I) being significant of such a condition in the subject (in comparison to normal cell controls, samples from melanoma and leukemia patients displayed abnormal profiles, p. 72, column 2, lines 20-31, p. 74, column 2, lines 1-15, and Figure 4, panels 1 and 2, and Figure 5, left panels).

With regard to claim 31, Even teaches a method for in vitro diagnosis characterized in that the condition is an auto-immune disease, B cell lymphoma or an immunodepressive disease (samples were studied from patients with primary malignant melanoma, acute graft versus host disease (aGVHD) and rheumatoid arthritis (Abstract and p. 67, column 1, lines 7-15).

With regard to claim 32, Even teaches a method for in vitro diagnosis, characterized in that the condition results from a bone marrow transplantation (samples were from a patient with aGVHD who also underwent an HLA-matched allogeneic bone marrow transplant, p. 67, column 1, lines 27-34, p. 72, column 2, lines 33-40).

With regard to claim 33, Delassus teaches a method for the in vitro follow-up of a treatment of a condition associated with an abnormal expression of the repertoire of a

given type of an immunoglobulin heavy chain by a lymphocyte B population in a subject, characterized in that it comprises the following steps:

(1) optionally, determining before the treatment the quantitative and qualitative profile of the given type of immunoglobulin heavy chain from a tissue sample of said subject according to anyone of claims I to 19 (profiles of β–chain repertoires were determined from cDNA obtained from total RNA by reverse transcription by amplification using one of 24 Vβ subfamily-specific primers and one Cβ-specific primer, and quantified using a run-off assay (p. 69, column 2, lines 5-22 and Table I; control samples from donors were tested to establish control Vb profiles, p. 72, column 2, lines 33-39),

(2) determining, during the treatment, the quantitative and qualitative profile of the given type of immunoglobulin heavy chain at given times from tissue samples of said subject according to anyone of claims 1 to 19 (profiles of β–chain repertoires were determined from cDNA obtained from total RNA by reverse transcription by amplification using one of 24 Vβ subfamily-specific primers and one Cβ-specific primer, and quantified using a run-off assay (p. 69, column 2, lines 5-22 and Table I; samples were tested after bone marrow transplant, p. 72, column 2, line 33 to p. 74, column 2, line 7),

(3) comparing the quantitative and qualitative profiles obtained at the step (2) and optionally at the step (1) with each others and optionally with a control quantitative and qualitative profile of the given type of immunoglobulin heavy chain, the demonstration of a significant modification of the profile obtained at the step (1) being significant of such

a condition in the subject (profiles of donor control and patient samples were compared, p. 74, column 2, lines 1-49 and Figure 5).

With regard to claim 34, Even teaches a method for in vitro follow-up characterized in that the condition is an auto-immune disease, a B cell lymphoma or an immunodepressive disease (samples were from a patient with aGVHD who also underwent an HLA-matches allogeneic bone marrow transplant, p. 67, column 1, lines 27-34, p. 72, column 2, lines 33-40).

With regard to claim 35, Even teaches a method for in vitro follow-up characterized in that the condition results from a bone marrow transplantation (samples were from a patient with aGVHD who also underwent an HLA-matched allogeneic bone marrow transplant, p. 67, column 1, lines 27-34, p. 72, column 2, lines 33-40).

With regard to claim 40, Even teaches the use of reagents for in vitro diagnosis of a condition associated with an abnormal expression of the repertoire of a given type of a T-cell receptor by a T lymphocyte population in a subject (p. 67, column 1, lines 7-15; profiles of β–chain repertoires were determined from cDNA obtained from total RNA by reverse transcription by amplification using one of 24 Vβ subfamily-specific primers and one Cβ-specific primer, and quantified using a run-off assay, p. 69, column 2, lines 5-22 and Table I).

With regard to claims 41, Even teaches the use of reagents for in vitro diagnosis of a condition such as auto-immune disease, a B cell lymphoma or an immunodepressive disease (profiles of β–chain repertoires were determined from cDNA obtained from total RNA by reverse transcription by amplification using one of 24 Vβ

subfamily-specific primers and one Cβ-specific primer, and quantified using a run-off assay, p. 69, column 2, lines 5-22 and Table I; samples were studied from patients with primary malignant melanoma, acute graft versus host disease (aGVHD) and rheumatoid arthritis (Abstract and p. 67, column 1, lines 7-15).

With regard to claim 42, Even teaches the use of reagents for in vitro diagnosis of a condition resulting from a bone marrow transplantation (profiles of β–chain repertoires were determined from cDNA obtained from total RNA by reverse transcription by amplification using one of 24 Vβ subfamily-specific primers and one Cβ-specific primer, and quantified using a run-off assay, p. 69, column 2, lines 5-22 and Table I; samples were from a patient with aGVHD who also underwent an HLA-matched allogeneic bone marrow transplant, p. 67, column 1, lines 27-34, p. 72, column 2, lines 33-40).

Even does not teach methods for determining the quantitative and qualitative profiles of a given type of immunoglobulin heavy chain expressed by a lymphocyte B population, but rather teaches methods for determining the quantitative and qualitative profiles of β chain repertoires expressed by T lymphocyte populations.

It would have been prima facie obvious to one having ordinary skill in the art at the time the invention was made to combine the methods of Delassus for PCR analysis of the immunoglobulin heavy chain repertoire and similar methods taught by Even for analysis of T-cell receptor β-chain repertoires since Even also applies the repertoire analysis techniques to comparing healthy and diseased human tissue samples for evidence of oligoclonal expansion in the diseased samples. Thus, an ordinary

practitioner would have been motivated to combine the methods of Delassus and Even to apply the methods of Delassus for repertoire determination for immunoglobulin heavy chains to the applications taught by Even, since the methods are essentially the same, and thus a wide variety of diseased tissue samples can be analyzed for both T-cell and B-cell abnormalities or variations of expression that have important implications for clinical diagnosis and research (see Abstract).

Conclusion

16. Claims 1-7, 15-18, 21-23, 30-35, and 40-45 are rejected. No claims are allowable.

Correspondence

17. Any inquiry concerning this communication or earlier communications from the examiner should be directed to David C. Thomas whose telephone number is 571-272-3320. The examiner can normally be reached on 5 days, 9-5:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached on 571-272-0782. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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